REMARKS

Claims 1 – 20 are pending in the application. Claim 11 has been cancelled.

A. Restriction Requirement

The Examiner has requested the cancellation of claims 8, 11 and 16. However, applicants believe that the cancellation of claims 8 and 16 should not be required in that they are drawn to the elected invention. Claim 8 states that "the surrounding external medium is air." The applicants elected the fluorocarbon gas perfluorobutane and the modifier gas oxygen. Claim 8 states that the external medium is "air" and does not relate to the "modifier gas." Thus, claim 8 should not be cancelled since it is part of the elected invention. Claim 16 states that the microbubble further comprises a membrane. This too is part of the elected invention and should not require cancellation.

B. Double Patenting Rejection

Claims 1 – 7, 9 – 10, 12 – 15 and 17 – 20 stand rejected under the judicially created doctrine of obviousness type double patenting over certain claims of U.S. Patent Nos. 6,372,195, 6,258,339, 5,695,741, 5,639,443, 5,798,091, and 5,805,162 and 6,193,952. Applicants are uncertain of the final scope of the claims of this application and respectfully request to revisit the issue of double patenting after the claims are allowed.

C. Rejection of the claims under 35 USC 103(a) over Schneider in view of Tickner

Claims 1 - 6, 9 - 10, 13 - 15, 17 - 18 and 20 stand rejected under 35 USC 103(a) as being unpatentable over Schneider in view of Tickner. Applicants respectfully disagree.

The Examiner asserts that Schneider teaches the use of C_4F_{10}. The Examiner is correct in that a search of the Schneider file wrapper shows that claim 1 mentions C_4F_{10} as of its filing date, applicants' attorney stands corrected. However, Schneider in view of Tickner does not obviate

claims 1 – 6, 9 – 10, 13 – 15, 17 – 18 and 20.

To properly establish a *prima facie* case of obviousness, three basic criteria must be met. First, there needs to be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings of the prior art. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all of the claim limitations. MPEP 706.02(j); In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438 (CAFC 1991). As will be explained below, the PTO has not met their burden in establishing a proper *prima facie* obviousness rejection of the claims over Schneider in view of Tickner.

1. The Schneider Patent (U.S. Patent No. 5,413,774)

As stated previously in response to the prior office action, Schneider mentions gas mixtures generally but never teaches anywhere in the specification a gas mixture containing a fluorocarbon gas and a modifier gas. In fact, Schneider clearly teaches away from such a combination. Schneider is entirely concerned about microbubble longevity, echogenicity and resisting arterial pressure and achieves this by teaching the replacement of air in the microbubbles with the use of fluorinated gases or halogenated hydrocarbon gases with low water solubilities. Schneider clearly teaches away from the use of air or its components in microbubbles.

For example, Example 1 teaches that after making air-filled albumin microvesicles according to the teachings of EP-A-324 938, that air be replaced by various fluorinated and halogenated hydrocarbon gases:

> For obtaining microballoons filled with other gases, the albumin solution was first purged with a new gas, then the foregoing operational sequences were effected under a stream of this gas flowing on the surface of the solution; then at the end of operations, the suspension was placed in a glass bottle and extensively purged with the desired gas before sealing.

(Col. 8, lines 50 – 57 of Schneider)

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> From the results of Table 1, it is seen that the critical pressure PC increases for gases of lower solubility and higher molecular weight. It can therefore be expected that microvesicles filled with such gases will provide more durable echogenic signals in vivo. It can also be seen that average bubble size generally increases with gas stability.

(Col. 9, lines 19 – 25 of Schneider)

Example 1 therefore teaches that to achieve critical pressure increases in microbubbles to create a worthwhile microbubble for ultrasound imaging, it is critical to utilize gases of low water solubility and higher molecular weight *instead* of air or its components.

In Example 2 of Schneider, the results of which are displayed in Table 2, the microbubbles made according to the teachings of Example 1 were tested by *in vivo* injection into the jugular vein of rabbits by imaging of the left and right heart ventricles. The duration of contrast enhancement was determined by recording the ultrasound signal for a period of time. Table 2 demonstrates that gases with high critical pressures had the greatest duration *in vivo* (i.e., sulfur hexafluoride, > 60 second duration) and gases with low critical pressure (e.g. air, 10 – 11 second duration) had the lowest *in vivo* duration and are therefore least preferred.

Example 3 compared the echogenic signals from ECHOVIST^{Tm}, a galactose microparticle filled with air, with the air evacuated and replaced with sulfur hexafluoride in the same ECHOVIST^{Tm} microparticle. As stated in Example 3, "it can be seen that sulfur hexafluoride, an inert gas with low water solubility, provides echogenic suspensions which generate echogenic signals stronger than comparable suspensions filled with air." Col. 10, lines lines 31 – 34 of Schneider. As in previous Examples 1 and 2, Example 3 demonstrates the superiority of contrast agents when using low solubility fluorinated gases in comparison to air and expressly teaches away from the use of contrast agents using air. The last sentence of Example 3 mentions that the teaching of prior art references EP-A-441-468 and EP 357 163 disclose certain echography compounds filled with gases including sulfur hexafluoride, but fail to understand the advantages of using sulfur hexafluoride in microbubbles. This is more support for the position that the overall point of the Schneider patent is the advantages of using low

solubility fluorinated compounds rather than air or individual components or air.

Example 4 compares various gas-filled microbubbles to determine a microbubble's resistance to pressure. As stated in Example 4, "the foregoing results indicate that the highest resistance to pressure increases is provided by the most water-insoluble gases" (column 11, lines 26 – 34 of Schneider). Thus, as in Examples 1 - 3, Example 4 teaches away from the use of air or its components in the use of microbubbles for contrast agents and instead teaches toward the use of water-insoluble gases.

Example 5 also demonstrates that water insoluble gases, such as fluorinated gases, provide a contrast agent with the longest duration, while soluble gases, such as air and its components, provide contrast agents of shorter duration and thus are the poorest choice of a gas. Examples 6 - 8, for reasons stated in the previous amendment, also reinforce the overall teachings of Schneider that replacing air with water insoluble gases, particularly fluorinated gases, provide far superior gases for use in ultrasound contrast agents.

Thus, there is absolutely no teaching or suggestion in Schneider to make a contrast agent with a fluorinated compound in combination with a modifier gas. In fact, Schneider expressly teaches away from such a combination and instead teaches the use of water insoluble gases for use in microbubbles. Further, if there is any suggestion of gas mixtures in the claims, Schneider teaches a mixture of fluorinated compounds, not a fluorinated compound and a modifier gas. The claims of Schneider, which uses the phrase "gas mixture", list only fluorinated gases.

2. Tickner (U.S. Patent No. 4,265,251)

As stated in the prior office action, there is no teaching or suggestion in Tickner of gaseous mixtures employing a fluorocarbon gas and a modifier gas. Tickner teaches methods of determining pressure within a liquid containing vessel. Tickner teaches the use of solid precursors (i.e., saccharide shell) injected into the blood stream wherein the solid precursors have an interior space filled with a gas in a pressure above that which exists in the cardiovascular system. After the saccharide shell dissolves after being injected, the gas escapes, forming a *free* microbubble inside the bloodstream with no membrane. Tickner, Col. 3, lines 6 – 32. As stated

by the Examiner, Tickner exemplifies carbon dioxide, but briefly mentions nitrogen, oxygen, argon, xenon, air, methane, freon, ether and carbon monoxide as substitute gases. However, there is nothing in Tickner that suggests its combination with the teachings of Schneider and nothing that suggests gas mixtures of a fluorocarbon gas and a modifier gas.

As stated previously, to properly combine references in an obviousness rejection, there needs to be some suggestion or motivation, either in the references themselves or in the knowledge generally available, to modify or combine the references of Schneider and Tickner. Schneider expressly teaches the use of low solubility fluorinated gases for use in microbubbles and expressly teaches away from the use of air or its components as a gas in a microbubble for use in ultrasound imaging. Tickner exemplifies the use of free gas carbon dioxide, a highly soluble gas. Thus one or ordinary skill in the art at the time of the present application's earliest priority date, in reading Schneider, would not have been motivated to create a microbubble with a gas mixture employing a fluorocarbon and a modifier gas. Further, there would also have been no expectation of success in combining the teachings of Schneider in view of Tickner even if properly combined. Schneider teaches against the use of soluble gases for use in a microbubble while Tickner exemplifies the soluble gas carbon dioxide.

The Examiner states in paragraphs 9 and 10 of the Office Action "that the gases recited in Tickner would functionally provide the same results when used in contrast agents." However, Schneider provides very clear evidence that many of the gases in Tickner would not functionally provide the same results.

Finally, the prior art references do not teach or suggest all of the claim limitations. There is no teaching in either Schneider of Tickner of a microbubble that "grows and shrinks to maintain osmotic equilibrium with the physiological gas saturation of the external medium." Thus it is unclear how Schneider in view of Tickner, even if properly combined, obviate the claimed invention.

For the above stated reasons, Schneider in view of Tickner does not obviate claims 1 - 6, 9 - 10, 13 - 15, 17 - 18 and 20 and applicants respectfully request withdrawal of the rejection.

D. Rejection of the claims under 35 USC 103(a) over Schneider in view of Unger

Claims 1 – 6, 9 – 10, 13 – 15, 17 – 18 and 20 stand rejected under 35 USC 103(a) as being unpatentable over Schneider in view of Unger (U.S. Patent No. 5,205,290). The Schneider reference has already been discussed at length. Regarding Unger, the Examiner states that "the particular problem was whether oxygen and perfluorobutane can be mixed together for *in vivo* application" and that "Unger was used to show that mixing oxygen and perfluorobutane for in vivo use had already been achieved" (paragraph 15 of the Office Action). Applicants respectfully disagree that Unger makes any such showing.

Unger teaches how to make microspheres by filling the microsphere with a gas or volatile liquid which expands the microsphere upon heating to create an expanded microsphere. These teachings are specifically found in column 4, lines 9 – 65 and column 5, lines 10 – 27 of Unger. In Example 6, Unger mentions replacing volatile liquid isobutane with the perfluorocarbon "liquid" (C_4F_{10}). However, C_4F_{10} would in fact be a gas at this temperature unless performed under pressure, which Example 6 never mentions. Regardless, the subsequent heat expansion process taught in Unger (150 ° C for 30 minutes; see Example 1) would cause any C_4F_{10} to boil off leaving an expanded microsphere but without containing C_4F_{10}. Thus Unger does not show that "mixing oxygen and perfluorobutane for *in vivo* use had already been achieved" in that there is no teaching in Unger of any *in vivo* use of perfluorobutane in a microsphere or microbubble and no teaching of perfluorobutane and oxygen together. The only use of C_4F_{10} in Unger is as a "volatile liquid", not as a gas contained in a microbubble during *in vivo* imaging.

There is no motivation in either Schneider or Unger for their combination. Schneider is concerned with ultrasound contrast agents. Unger is concerned with methods and the compounds used for inflating plastic microspheres for use in creating homogenous aqueous suspensions for ingestation by a patient for CT imaging of the gastrointestinal tract. Further, even if properly combined, there is nothing in Schneider in view of Unger that would lead one of ordinary skill in the art to applicants' claimed invention. Applicants respectfully request

withdrawal of the rejection of claims 1 – 6, 9 – 10, 13 – 15, 17 – 18 and 20 of Schneider in view of Unger.

Applicants have filed a Request for Continued Examination and the fee payable for such action. Applicants have also filed for a three month extension of time. If there are any questions concerning this submission, applicants' attorney can be reached at the number stated below.

Respectfully submitted,

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